EFFECT OF ORAL CLONIDINE PREMEDICATION ON HEMODYNAMIC RESPPONSE TO LAPROSCOPY

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CERTIFICATE

This is to certify that the dissertation entitled, **"EFFECT OF ORAL CLONIDINE PREMEDICATION ON HEMODYNAMIC RESPPONSE TO LAPROSCOPY"** submitted by **Dr. L.KAVYA** in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr. M.G.R Medical University, Chennai is a bonafide record of the work done by her in the Institute of Anaesthesiology and Critical Care, Madras Medical College, during the academic year 2008 – 2011

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INTRODUCTION

Laparoscopic surgery is a technique with cosmetic advantage, reduction of hospital days, postoperative pain and morbidity. However laparoscopy also induces certain pathophysiological hemodynamic changes in response to pneumoperitoneum ,which include an increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance. Treating patients with clonidine blunted the increase in mean arterial pressure, systemic vascular resistance and the release of catecholamines. (1) Considering this, the present study was designed to evaluate the type and extent of haemodynamic changes associated with laparoscopic surgery and to find out the efficacy of clonidine in prevention of such changes. The results of the study can promote further evaluation and usage of the drug for laproscopy in patients with compromised cardiovascular system.

AIM OF THE STUDY

To evaluate the efficacy of oral clonidine premedication in blunting hemodynamic response to pneumoperitoneum in laproscopic surgeries.

THE HEMODYNAMIC RESPONSE TO PNEUMOPERITONEUM

Laparoscopy is endoscopic visualization of the peritoneal cavity usually assisted by a pneumoperitoneum that distends and separates the abdominal wall from its contents. CO2 gas insufflation is preferred by most laparoscopists because it has a high diffusion coefficient and is a normal metabolic end product rapidly cleared from the body. Also, CO2 is highly soluble in blood and tissues and does not support combustion.

The cardiovascular system is one of the most challenged systems of the human body during laparoscopy. Changes occurring during CO2 pneumoperitoneum result from two main factors:

- Hypercarbia (and the subsequent acidosis)
- Increased intra-abdominal pressure.

CO2 is highly soluble and therefore is very rapidly absorbed from the peritoneal cavity into circulation. Because absorbed CO2 can only be excreted through the lungs, hypercarbia can only be avoided by a compensatory hyperventilation by increasing the tidal volume of ventilation in anesthetized patients. Hypercarbia can also develop as a result of an insufficiently exhaustion of CO2. Absorption of CO2 is increased particularly during

prolonged surgery using high intra-abdominal pressure. Exhaustion of CO2 is reduced in patients with compromised cardiopulmonary function and restricted CO2 clearance . Also, the compensatory hyperventilation is impeded by the Trendelenburg position or a high intraabdominal pressure, which cause a cephalad displacement of the diaphragm (resulting in reduction of lung volumes) and a restriction in diaphragmatic mobility. In these conditions, severe hypercarbia can develop despite aggressive hyperventilation.

Hypercarbia and acidosis can cause hemodynamic changes by direct action on the cardiovascular system and by an indirect action through sympathoadrenal stimulation. The direct effect of carbon dioxide and acidosis can lead to decreased cardiac contractility, sensitization of myocardium to the arrhythmogenic effects of catecholamines and systemic vasodilatation. The centrally mediated, autonomic effects of hypercarbia lead to a widespread sympathetic stimulation resulting in tachycardia and vasoconstriction.

It should be stressed that intra-abdominal pressure has a major role in the development of hypercarbia since it both increases the absorption and decreases the exhaustion of CO2. Increased intra-abdominal pressure during pneumoperitoneum triggers several pathophysiological mechanisms independently of the type of used gas. The most important mechanism is neurohumoral . Humoral response causes release of vasopressin and activation

of renin-angiotensin-aldosterone. The sympathetic stress response(neural) , causes tachycardia and hypertension. The increased intra-abdominal pressure also leads to a mechanical impairment of the venous return thus decreasing the cardiac preload. Depending on the extent of above mentioned mechanisms there will be an increase in systemic vascular resistance and pulmonary vascular resistance resulting in an increased afterload and the final outcome depends on the functional reserve of the heart.

Joris et al 5, using invasive monitoring, observed a significant increase in mean arterial pressure (35%) after peritoneal insufflations, along with an increase of systemic vascular resistance (65%) and pulmonary vascular resistance (90%), and a decrease in cardiac index (20%), while the pulmonary capillary wedge pressure and central venous pressure increased.

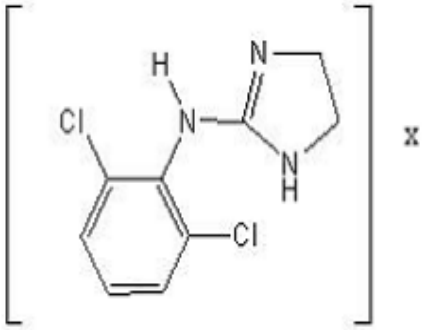
The measures suggested to prevent and treat the cardiovascular complications are

- Preloading with about 10ml/kg of crystalloid, to improve the cardiac preload.
- Intermittent pneumatic compression of lower limbs, to increase venous return and preload.

- Avoiding extreme positioning, as it affects both cardiac preload and ventilation.
- Slow insufflation.
- Maintaining lower intra-abdominal pressures.
- Maintaining normocarbia.
- Tilting the patient after insufflation.
- Pharmacological therapy (α-2 agonists, β- blockers, vasodilators, remifentanyl etc)

PHARMACOLOGY OF CLONIDINE

Clonidine Hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The following is the structural formula:



Pharmacodynamics:

Clonidine produces clinical effects after binding to α2-adrenergic receptors, of which there are three subtypes (α 2A, α2B, and α2C). Because of an imidazole ring in its structure, this compound also interacts with the imidazoline receptor. Clonidine can produce either hypotension or hypertension. At lower doses, the dominant action is sympatholysis, i.e., the ability to block the sympathetic arm of the autonomic nervous system, which is mediated by the α 2A-adrenergic receptor subtype. At higher doses, the hypertensive action

,

dominates via the activation of α2B adrenoceptors, located on smooth muscle cells in the resistance vessels.

In the heart, the dominant action is a decrease in tachycardia (through block of the cardioaccelerator nerve) and bradycardia (through a vagomimetic action).

On the central nervous system, it excerts following actions- sedation, hypnosis, analgesia, anxiolysis, cognitive enhancement etc..

Pharmacokinetics:

Oral clonidine is well absorbed and used completely in the body. The pharmacological effect of clonidine appears in about 1.5 hours, with the peak level in 3 hours. The patient's blood pressure declines within 30 to 60 minutes after an oral dose, the maximum decrease occurring within 2 to 4 hours. The half life is approximately 8.5±0.9hours. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact; therefore, orthostatic symptoms are mild and infrequent. . Neither food nor the race of the patient influences the pharmacokinetics of clonidine.

Clonidine is highly lipid soluble and easily crosses the blood brain barrier, interacting with alpha-adrenergic receptors at the spinal and supraspinal

sites. Following oral administration about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. In patients with renal impairment half-life can increase upto 41 hours. About 50% of the absorbed dose is metabolized in the liver.

USES:

Clonidine, was first introduced into clinical practice (in the1970s), as an antihypertensive medication, which forms the bulk of its use, even now. The drug has also been used to treat dysmenorrhoea, hot flushes that occur with menopause, attention deficit hyperactivity disorder (ADHD), and withdrawal symptoms from dependence on narcotics, alcohol, or nicotine (smoking).

It has found lot of use perioperatively. It attenuates hypertension, tachycardia, and catecholamine release in response to stress induced by anaesthetic and surgical procedures,(e.g) Laryngoscopy, peritoneal insufflation etc. The drug has been used for anaesthetic premedication, providing sedative, anxiolytic, and analgesic effects . It decreases the requirements for both IV and volatile anaesthetics. It also reduces post operative shivering, nausea and vomiting. It has also been proved to decrease perioperative myocardial ischaemia by reducing the myocardial work. Time for post operative analgesic requirement is prolonged and better sedation scores obtained with clonidine.

SIDE EFFECTS:

Most commonly reported side effect is dry mouth or xerostomia, followed by dizziness, drowsiness, constipation and sedation.

Adverse effects have been reported as an extension of its pharmacologic profile (i.e., hypotension, bradycardia, and hypertension).

Other very rare side effects are paresthesia, abdominal pain, nausea, urticaria, urinary retention, erectile dysfunction, gyaenecomastia etc and they don't occur with a single dose given preoperatively.

DRUG INTERACTIONS:

Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs.

If a patient receiving clonidine hydrochloride is also taking tricyclic antidepressants, the hypotensive effect of clonidine may be reduced, necessitating an increase in the clonidine dose.

Clonidine when used concomitantly with agents known to affect sinus node function or AV nodal conduction, e.g., digitalis, calcium channel blockers, and beta-blockers, Sinus bradycardia can occur.

CONTRAINDICATIONS:

The only absolute contraindication is allergy to the drug.

Clonidine should be used with caution in patients with

- Severe coronary insufficiency
- Conduction disturbances
- Recent myocardial infarction
- Cerebrovascular disease or chronic renal failure.

It is also not used in pregnant, lactating and paediatric population.

MATERIALS AND METHODS

This interventional study was done in fifty patients undergoing elective laproscopic surgery either appendicectomy or cholecystectomy under general anaesthesia. It is a prospective randomised single blinded study.

Institutonal ethical committee approval was obtained and written informed consent was obtained from all patients. The study was conducted during the period from may 2010 to july 2010, in the Institute of Anaesthesiology and Critical care, Govt General Hospital, Chennai. The surgeries were done in general surgery theatre complex of the hospital.

INCLUSION CRITERIA:

- Patients of both sexes.
- ASA Physical Status 1-2.
- Age 16- 65 years.

EXCLUSION CRITERIA

- Diabetics
- Hypertensives
- Patients with Ischaemic Heart Disease

- COPD patients/ Asthmatics
- Patients with known allergy to drugs used in the study.
- Patients with difficult airway.
- Patients on concomitant drugs like MAO inhibitors, methyl dopa, benzodiazipines,beta blockers etc.
- Patients with increased intracranial tension/
- Patients with renal impairment.
- Those with A-V block and severe valvular insufficiencies.

MATERIALS:

- Oral Clonidine 150µg tablets / Plecebo- Multi Vitamin tablets
- Routine Anaesthetic Equipments
- Drugs-Inj.Fentanyl, Inj.Ranitidine, Inj.Metaclopromide, Inj.Propofol, Inj.suxamethonium, Inj. Vecuronium, Inj.Neostigmine, Inj. Glycopyrrolate, IV Fluids and Emergency drugs.
- Monitors – ECG, SPO2, NIBP , ETCO2 , intra-abdominal pressure.

METHOD:

All patients underwent minimum investigations – haemoglobin, renal function tests, chest X-ray and electrocardiogram. Pre-operative assessment was done for all patients in Central anaeathesic Assessment Room(CAR). Patients belonging to ASA physical status 1 or 2 were only selected for the study.

Patients selected for the study were randomized into two groups- Group P(placebo) and Group C (Clonidine)

On the morning of surgery, patients were given either oral clonidine 150µg tablet (Group C) or Multivitamin tablet (Group P) with about 30 to 60 ml of clear water. Before the intake of study drug baseline heart rate, systolic, diastolic, and mean arterial pressures were measured. Patients were shifted to a calm room where they were observed. Intravenous access was obtained and they were preloaded with 10 ml/kg of Ringer Lactate solution.

About 90 minutes after that they were shifted to the operating table. The monitors used were, Electrocardiograph, Pulse oximetry, blood pressure by automated oscillometry. After intubation, End Tidal CO2 and after induction of pneumoperitoneum, intra abdominal pressure was monitored. The drugs used and anaesthetic technique was standardized for both groups.

Premedication:

- Inj.Ranitidine 50mg and Inj.Metaclopromide 10mg were given i.v to avoid post operative nausea and vomiting, which is very common in laproscopic surgeries.
- Inj.fentanyl 2µg/kg i.v for analgesia
- Inj. Glycopyrrolate 0.2mg i.v for antisecretory action.

Preoxygenation:

Done for three minutes with 4 lit/min of 100% 02.

Induction:

With 2mg/kg Inj. propofol and 1.5 mg/kg Inj. Succinyl choline 1.5 mg/kg i.v

Intubation:

Appropriate size laryngoscope blade and appropriate size cuffed endotracheal tube was used. None of the patients had a predicted difficult airway and intubation in all patients was done in a single attempt with ease by the same investigator. Soon after the endotracheal tube was secured, a nasogastric tube was inserted and bladder was catherised for all patients.

Maintenance:

Nitrous oxide was used in a concentration of 66% with Oxygen 33% . Inj. Propofol infusion at the rate of 3mg/kg/hr was used for maintenance of anaesthesia. It was started soon after induction and terminated at the time of desufflation of pneumoperitoneum. For muscle relaxation inj. Vecuronium 0.1mg/kg i.v was given followed by 1mg i.v everytime the neuromuscular action recovered. Intra operative hydration was maintained with Ringer Lactate.

Ventilation was done such that all patients had ETCO2 between 35-40 mmHg throughout the procedure.

Surgical procedure:

The selected patients underwent either appendicectomy or cholecystectomy by laproscopy. After induction and intubation bladder was catheterised and then abdomen painted and draped. Pneumoperitoneum was created with insufflations of CO2 through Verre's needle in the supraumbilical region following which the surgery was proceeded with. The intra- abdominal pressure was strictly below 14 mmHg and was maintained between 12-14mmHg. The average duration of surgery was 54.34 min for appendicectomy and 90.46 min for cholecystectomy.

Reversal and extubation:

At the end of surgery, neuromuscular blockade was reversed with 50µg/kg of Inj. Neostigmine and 0.2 mg of Inj.glycopyrrolate for every mg of neostigmine. Patients were extubated after recovery of airway reflexes and consciousness and thorough oral suctioning. Patients were shifted to recovery room, given supplemental Oxygen via mask and observed for two hours after which patients were shifted to post-operative ward.

Outcome measures:

Through the surgery, the study outcome measures (i.e) the haemodynamic variables – heart rate, systolic, diastolic, and mean arterial pressures were noted at these times -

1. On table- before induction.
2. Just after intubation
3. 5 min after intubation
4. 5 min after insufflation
5. 15 min after insufflation
6. 30 min after insufflation

7. After extubation

The incidence of complications in hemodynamic parameters, (hypotension, bradycardia, hypertension), and the need for treatment was also noted in both groups. They were defined and treated as follows;

A mean arterial pressure of less than 60mmHg was considered hypotension and was treated with i.v bolus of 6 mg ephedrine, which was repeated as needed.

A heart rate of less than 50 beats/ min was considered as bradycardia and was treated with 0.6mg i.v bolus of Atropine.

A mean arterial pressure of more than 120mmHg lasting more than five minutes was treated with intravenous infusion of nitroglycerin 5μg/kg/hr.

REVIEW OF LITERATURE

In a study by Y.Passi et al(2009) fifty adult patients belonging to ASA physical status I or II, scheduled for laparoscopic Cholecystectomy were randomly allocated to two groups . Group A (clonidine) received Tab. clonidine 150µg orally and Group B (Control) received Tab. vitamin B complex orally as premedication 60-90 minutes before scheduled laparoscopy. Heart rate and mean blood pressure were recorded prior to intubation, 15 min after endotracheal intubation, at skin incision, 15 min and 30 min after creation of pneumoperitoneum and 15 min after release of pneumoperitoneum. Anaesthetic technique was standardized , normocapnia and safe intra abdominal pressure (12-14 mmHg) maintained. Heart rate and mean arterial pressure was significantly low in the clonidine group at all instances except prior to intubation. One patient each developed bradycardia and hypotension in Group A which was managed with Inj.Atropine 0.5 mg and Inj. Ephedrine 6mg boluses respectively. Hypertension occurred in 9 patients in the group B and was managed with increase in concentration of Isoflurane and antihypertensive drugs e.g. Inj. NTG or Inj. esmolol as infusion i.v. They concluded that oral clonidine 150 µg 60- 90 min before scheduled laparoscopic cholecystectomy provides stable hemodynamics and protection against stress response triggered by pneumoperitoneum.

M. Das et al did a similar study in Indian population in 2007.Sixty adult patients of ASA physical status I & II, scheduled for elective laparoscopic cholecystectomy were randomly allocated to one of the two groups to receive either oral clonidine 150 µg (Group C) or ranitidine 150 mg (Group P), 90 minute before induction of anaesthesia. Anaesthetic technique and intra abdominal pressure were standardized. Systemic arterial pressure including the systolic, diastolic and mean arterial pressure, heart rate were recorded at the following points of time : (1) prior to induction (2) three minutes after endotracheal intubation (3) before pneumoperitoneum (4) fifteen minutes after pneumoperitoneum (5) thirty minutes after pneumoperitoneum(6) ten minutes after release of CO2 and (7) ten minutes after extubation. Significant rise in heart rate was observed following pneumoperitoneum in control as compared to Clonidine group.(99.23±14.02 Vs 81.26±8.40 bpm). Similarly, rise in systolic arterial pressure(143.63±19.60 Vs 119.6±10.06mm Hg), diastolic arterial pressure (99.23±14.02 Vs81.26±8.40 mm Hg) and mean arterial pressure (114.13±16.57 Vs 93.83±8.107 mm Hg) was more in control group following pneumoperitoneum. Ten patients (33.3%) in placebo group received nitroglycerine infusion (0.5 µg.kg-1 .min-1) for treatment of intraoperative hypertension. It was not required in the clonidine group.

Sunita Goel and Manju Sinha from Bombay Hospital(2006) conducted a similar study. They gave 100 μg oral clonidine as premedication one hour before major laproscopic gyaenecologic surgeries in 50 patients and compared it with placebo in another 50 patients. They compared the hemodynamic variables at induction, intubation, 5 min, 10 min, 30 min 60 min during surgery and at extubation.

The clonidine group had statistically significant low pulse rate, systolic and diastolic blood pressure on induction and 5, 10 mins post gas insufflation. The haemodynamics at 30 mins, 60 mins and at extubation were almost comparable and no significant difference was noted. There was a significant fall in pulse rate and systolic blood pressure in clonidine group at 5, 10 mins post insufflation as compared to baseline which was not seen in the control group. Forty patients of the non- clonidine group required esmolol or propofol as infusion, intraoperatively to maintain the pressures within the constraints of the aim of the study. They administered glycopyrrolate 0.2 mg for 3 patients when there was bradycardia of 50/min or below in the clonidine group. They concluded that oral clonidine premedication is advantageous because of

- Decreased pressor response to laparoscopy and pneumoperitoneum
- Maintenance of haemodynamic parameters

- No side effects other than bradycardia which was easily treatable.

A. Islam et al(2008) studied the role of oral clonidine and atenolol in controlling tachycardia and hypertension associated with pneumoperitoneum with CO2 during laparoscopic cholecystectomy. Patients were divided equally into three groups, which were Group-I: Oral clonidine(150ìgm), Group-II: oral atenolol(25mg) and Group-III: placebo (vitamin-c tablet), twenty five patients were in each group. The premedication was given 60 to90 min prior to induction. They compared hemodynamic variables at various points- before induction, after intubation, after skin incision, after insufflation, 5 min, 10 min, 15 min, 20 min after insufflations. The mean pulse rate was significantly low in Clonidine premedicated patients at all points except just before induction and just after insufflations. The decline in pulse rate from induction through the surgery was also notably low in the Clonidine group. They didn't observe significant difference in the systolic, diastolic and mean arterial pressures, though there was a lowering of blood pressure in clonidine group. They noted that anaesthetic and analgesic requirement was less in Clonidine group and the recovery scores were almost similar in all three groups.

Sung et al(2000) from Taipei randomly allotted one hundred and ten patients, scheduled for elective laparoscopic cholecystectomy to either of the

placebo or clonidine group. Those in the clonidine group (n = 45) were premedicated with oral clonidine 150 micrograms 60- 90 mins prior to anesthesia. Normocapnia was maintained through out the procedure. Patients in the clonidine group displayed greater hemodynamic stability perioperatively and the isoflurane requirement was also reduced (30% less). The post operative analgesic requirement was also less in Clonidine treated patients.

Norimasa et al (2009) from Jichi medical university, Japan, used oral clonidine premedication and compared it against Atropine-hydroxyzine, for premedication in laproscopic cholecystectomy, 20 patients in each group .They concluded that oral clonidine has an anaesthetic sparing and hemodynamic stabilizing effect during laproscopic cholecystectomy.Heart rate in the clonidine group was significantly lower at various points during the surgery compared to the other group. They didn't observe a significant difference in the mean arterial pressures.

Yu et al, (2003) had done a study to investigate the clinical efficiency of oral clonidine premedication in anaesthesia and analgesia in 32 patients undergoing laproscopic cholecstectomy. Of them, 16 patients received oral clonidine 150 μg and rest 16 placebo control received oral antacid (alugelhydroxide 300 mg) before anaesthesia. They used heart rate variability

to quantify heart rate control at baseline, pneumoperitoneum and recovery periods. They found that oral clonidine preserved the heart rate control during pneumoperitoneum and recovery.

Yotsui et al(2001) from Japan, investigated the effects of oral administration of clonidine on sympathetic and endocrinological responses to laproscopic cholecystectomy. They did the study in twenty patients, 10 in the clonidine group- 4μg/kg and 10 in the control group- placebo, given 2 hours prior to surgery. The hemodynamic variables were observed perioperatively. Plasma concentrations of cortisol, ACTH, noradrenaline, adrenaline, and dopamine were determined before administration of clonidine or placebo, 2 h after the beginning of the operation, and 3 h after the end of the operation. Systolic and diastolic blood pressures were lower in the clonidine group than in the control group immediately after endotracheal intubation and extubation . Patients in the clonidine group showed lower plasma concentrations of noradrenaline 2 h after the beginning of the operation than patients in the control group. The plasma concentrations of the other hormones did not differ between groups.

Joris et al(1998) from American College of Cardiology investigated endocrine correlates of the hemodynamic changes induced by carbon dioxide

pneumoperitoneum (PNO) and also studied whether clonidine might modulate the hemodynamic changes induced by PNO by reducing release of catecholamines and vasopressin. Laparoscopy resulted in progressive and significant increases in plasma concentrations of cortisol, epinephrine, norepinephrine, vasopressin and renin. Clonidine significantly reduced mean arterial pressure, heart rate and the increase in systemic vascular resistance. Clonidine also significantly reduced catecholamine concentrations but did not alter vasopressin and cortisol plasma concentrations.

Javaherfroosh et al(2009) studied the efficacy of oral clonidine (0.2mg) in controlling post operative nausea and vomiting (PONV) in patients undergoing laproscopic gyaenecologic surgeries. Clonidine significantly reduced PONV and no case of significant hypoxemia, drop in blood pressure or heart rate was noted. Post operative pain scores were also less. They have recommended routine use of clonidine before Laproscopy.

Oh SW et al (2002) used intravenous Clonidine 150µg as premedication for Laproscopically assisted vaginal Hysterectomy. When compared with control group (saline), they observed a significantly lower pulse rate and blood pressure after insufflation in the clonidine group.

M.Uchida et al (2004) examined the hemodynamic responses to hypercapnia during propofol and isoflourane anaesthesia and compared them in presence and absence of Clonidine premedication- 5µg/ kg, 90 min prior to surgery. They measured mean arterial pressure, cardiac index, and heart rate at ETCO2 values of 35 and 55mmHg by adding CO2 to the inspired gas. All variables were significantly lower in the Propofol- Clonidine sub group than the other three sub groups. They attributed the results to a profound suppression of sympathoadrenal activity due to interaction between the basal anaesthetic and premedicant.

Talebi et al(2010) studied Effects of Oral Clonidine Premedication on Haemodynamic Response to Laryngoscopy and Tracheal Intubation. 274 ASA I and II subjects were randomly allocated to receive oral clonidine (0.2 mg) or placebo as premedication 90-120 min before induction. Both heart rate and systolic blood pressures were significantly higher in Control group at three subsequent measurements following intubation.

D L Raval et al(2002) used oral Clonidine - 4µg/ kg, 90 min prior to induction and found that it significantly blunted the pressor response to laryngoscopy and intubation.

STATISTICAL ANALYSIS

All data were collected, tabulated and expressed as Mean ± Standard Deviation. Statistical analysis was done with MINITAB software. All data were normal and stable. Hence, comparative analysis of the means of two groups was done by Two sample- T Test. The variances were compared by F- Test. P value of less than 0.05 was considered statistically significant.

OBSERVATION AND RESULTS

The demographic profile in both groups was comparable and no significant difference was observed.

AGE

Group	Mean(yrs)	Standard deviation	Statistical significance
Group –P	31.4	12.1	P =0.943
Group – C	31.6	11.6	

SEX

Group	Male	Female
Group P	11	14
Group C	12	13

All the patients belonged to ASA I physical status in both groups.

WEIGHT

Group	Mean(kg)	Standard deviation	Statistical significance
Group -P	56.2	7.37	P =0.586
Group - C	57.32	7.06	

SURGICAL PROCEDURE

Group	Appendicectomy	Cholecystectomy
Group P	18	7
Group C	17	8

The baseline hemodynamic variables before ingestion of premedication drug (Clonidine or placebo) were also comparable between the groups.

BASELINE HEART RATE

Group	Mean(bpm)	Standard deviation	Statistical significance
Group -P	82.5	14.3	P =0.967
Group - C	82.4	13.0	

BASELINE SYSTOLIC BLOOD PRESSURE

Group	Mean(mmHg)	Standard deviation	Statistical significance
Group -P	119.3	10.6	P =0.861
Group - C	119.8	10.3	

BASELINE DIASTOLIC BLOOD PRESSURE

Group	Mean(mmHg)	Standard deviation	Statistical significance
Group –P	79.44	7.52	P = 0.555
Group – C	78.12	8.1	

BASELINE MEAN ARTERIAL PRESSURE

Group	Mean(mmHg)	Standard deviation	Statistical significance
Group -P	92.52	7.41	P =0.913
Group - C	92.28	8.06	

HEART RATE

The mean heart rate was significantly low in Group C when compared with Group P at all points of time. ($P < 0.05$)

Time	Group	Mean	Standard deviation	Statistical Significance
On table After study drug	P	86.8	16.3	P - 0.003 (HS) F test - P - 0.672
	C	73	14.9	
Just after Intubation	P	100.9	13.9	P - 0.00* (HS) F test - P - 0.121
	C	76.7	10	
5 Min after Intubation	P	83.2	15.1	P - 0.00* (HS) F test - P - 0.203
	C	64	11.6	
5 Min after Pneumo peritoneum	P	79	15	P - 0.00* (HS) F test - P - 0.004
	C	63.08	8.11	
15 Min after Pneumo peritoneum	P	79.8	16.3	P - 0.00* (HS) F test - P - 0.001
	C	63.28	7.92	
30 Min after Pneumo peritoneum	P	78.5	15.4	P - 0.00* (HS) F test - P - 0.001
	C	63.8	7.57	
After extubation	P	95.4	15.8	P - 0.00 * (HS) F test - P - 0.383
	C	74.3	13.2	

SYSTOLIC BLOOD PRESSURE

The difference in mean systolic blood pressure was statistically significant (P<0.05) at all points from pre- induction to after extubation and Group P patients had higher values.

Time	Group	Mean	Standard deviation	Statistical Significance
On table After study drug	P	123.2	10.6	P - 0.00* (HS) F test - P - 0.131
	C	113.9	14.5	
Just after Intubation	P	141.6	19.8	P - 0.00* (HS) F test - P - 0.661
	C	115.4	18.1	
5 Min after Intubation	P	117.4	20.9	P - 0.003 (HS) F test - P - 0.013
	C	102.2	12.4	
5 Min after Pneumo peritoneum	P	139.16	11.4	P -0.00* (HS) F test – P -0.851
	C	121.84	10.2	
15 Min after Pneumo peritoneum	P	139.6	10.8	P - 0.00* (HS) F test - P - 0.04
	C	121.1	16.5	
30 Min after Pneumo peritoneum	P	136.4	13.9	P - 0.001 (HS) F test - P - 0.612
	C	121	15.5	
After extubation	P	139.6	13.7	P - 0.00* (HS) F test - P - 0.352
	C	121	11.3	

DIASTOLIC BLOOD PRESSURE

Clonidine premedicated patients (Group C) were found to have significantly low diastolic blood pressure values (P <0.05) when compared to the placebo group (Group P) at all points of time.

Time	Group	Mean	Standard deviation	Statistical Significance
On table After study drug	P	84.04	8.16	P - 0.00* (HS) F test - P - 0.425
	C	71.84	9.62	
Just after Intubation	P	96.6	18.4	P - 0.00* (HS) F test - P - 0.304
	C	73.6	14.9	
5 Min after Intubation	P	79.2	14.8	P - 0.001 (HS) F test - P - 0.107
	C	65.7	10.6	
5 Min after Pneumo peritoneum	P	98.88	9.8	P - 0.00* (HS) F test - P - 0.003
	C	77.5	18.4	
15 Min after Pneumo peritoneum	P	96.8	8.63	P - 0.00 * (HS) F test - P - 0.546
	C	80.1	10.7	
30 Min after Pneumo peritoneum	P	94.12	9.33	P - 0.00 * (HS) F test - P - 0.712
	C	80.8	10.1	
After extubation	P	92.72	8.47	P - 0.00 * (HS) F test - P - 0.654
	C	79.44	7.72	

MEAN ARTERIAL PRESSURE

Since systolic and diastolic blood pressures were lower, the mean arterial pressure was also significantly lower in Group C than in Group P (P <0.05) at all instances.

Time	Group	Mean	Standard deviation	Statistical Significance
On table After study drug	P	98.24	8.03	P - 0.00 * (HS) F test - P - 0.170
	C	86.4	10.7	
Just after Intubation	P	111.2	17.4	P - 0.00 * (HS) F test - P - 0.557
	C	87.7	15.4	
5 Min after Intubation	P	91.8	15.7	P - 0.001 (HS) F test - P - 0.069
	C	77.8	10.7	
5 Min after Pneumo peritoneum	P	111.9	9.6	P - 0.00 * (HS) F test - P - 0.065
	C	94.9	14.1	
15 Min after Pneumo peritoneum	P	110.56	7.91	P - 0.00 * (HS) F test - P - 0.033
	C	94	12.4	
30 Min after Pneumo peritoneum	P	107.76	9.73	P - 0.00 * (HS) F test - P - 0.451
	C	93.4	11.4	
After extubation	P	108.28	9.73	P - 0.00 * (HS) F test - P - 0.458
	C	93.12	8.34	

Review of literature indicates that hemodynamic perturbations during laproscopy occur most commonly at the start of pneumoperitoneum(20). With this in mind, the percentage change in hemodynamic variables between baseline values and the values noted at 5 min after insufflation was calculated and the mean values plotted.

After 5 min of pneumoperitoneum, heart rate was found to be lower than baseline in both groups but, the % decrease was steeper in Group C.

Systolic blood pressure and mean arterial pressure increased on insufflations, but the % increase from baseline was very meagre in Group C.

After insufflations, diastolic blood pressure was found to be higher than baseline in Group P whereas it was much lower than baseline in Group C

Group	Heart rate	Systolic blood pressure	Diastolic blood pressure	Mean arterial pressure
Group P	-7.27%	+13.95%	+19.03%	+16.97%
Group C	-31.4%	+0.02%	-24.8%	+1.12%

ADVERSE EVENTS

The incidence of adverse events in the form of extremes of the hemodynamic variables in both groups was noted.

Three patients in Group P developed hypertension which required treatment with Nitroglycerine infusion. None of the patients in Group C developed hypertension.

Three patients in Group C developed bradycardia and were treated with bolus dose of Inj.Atropine 0.6 mg i.v. One patient developed hypotension, and was given single bolus of Ephedrine 6 mg i.v. None of the patients in Group P developed bradycardia or hypotension.

INCIDENCE OF ADVERSE EVENTS

Event	Group P (No of patients)	Group C (No of patients)
Hypertension	3	0
Bradycardia	0	3
Hypotension	0	1

DISCUSSION

Pneumoperitoneum during laparoscopy produces significant haemodynamic changes, which can be detrimental especially in elderly and haemodynamically compromised patients. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum. This prospective study was carried out in 60 adult patients, to evaluate the effect of clonidine premedication in attenuating haemodynamic stress response associated with pneumoperitoneum.

The preferred anaesthetic technique for laproscopic surgery is general anaesthesia with muscle paralysis, tracheal intubation and intermittent positive pressure ventilation(20, 21). Although regional anaesthesia is possible, need for high level of blockade, high incidence of post operative shoulder pain, increased patient discomfort and anxiety, high minute ventilation needed to maintain normocarbia during spontaneous ventilation are disadvantages. All the patients in our study were given general anaesthesia with controlled ventilation.

Clonidine is completely absorbed after oral administration and clinical effect. The sympatholytic action starts manifesting by 30 to 60 min. Almost all the reference studies had given clonidine 60 to 90 min prior to surgery and in our study too clonidine was given at around the same time.

Adequate preoperative volume loading is an intervention with Grade A scientific evidence in preventing cardiovascular complications of laproscopy(22). All patients were preloaded with 10 ml/ kg Ringer Lactate.

Propofol was chosen for induction and maintenance of anaesthesia, because it was found to provide stable hemodynamics, fast recovery, and less post operative side effects during laproscopy(17,23,24). Vecuronium was the muscle relaxant of choice in this study, because of its cardiostable profile.

In ASA I-II patients, the haemodynamic and circulatory effects of a

12 - 14 mmHg capnoperitoneum are generally well tolerated(22). Following induction of pneumoperitoneum, the intra abdominal pressure was maintained below 14 mmHg and in the range of 12-14 mmHg.

Since hypercapnia is a major contributor to hemodynamic perturbations during pneumoperitoneum, patients were hyperventilated to maintain normocapnia (i.e) ETCO2 was maintained in the range of 35- 40 mmHg.

Demographic profile including age, sex, surgical procedure, weight were comparable between both groups. With regards to sex distribution in our study, males and females were almost equal in number. This is in contrast to other studies where females were more in number. The studies referred were done in

patients undergoing either cholecystectomy or gyaenecological surgeries, whereas our study included patients who underwent both cholecystectomy and appendicectomy, which can explain this difference.

The baseline hemodynamic variables (before ingestion of study drug-BSD) were comparable between the groups. 60-90 min after the study drug(ASD), heart rate(HR), systolic, diastolic and mean arterial pressures (SBP, DBP & MAP) were lower than the baseline in Group C, whereas it was higher in Group P.

	HR(bpm)		SBP (mmHg)		DBP(mmHg)		MAP(mmHg)	
	BSD	ASD	BSD	ASD	BSD	ASD	BSD	ASD
Group P(avg)	82.5	86.8	119.3	128.8	79.4	84.1	92.5	98.3
Group C(avg)	82.3	73.1	119.8	113.9	78.1	71.8	92.2	86.4

Intake of Clonidine had produced a considerable decrease in the variables after 60 to 90 min. Literature shows that the pharmacological effects

start appearing by 60 min(5, 10) which is well correlated here, and sympatholysis is manifested. The sedative- anxiolytic property of clonidine could also have contributed to this decrease noted preoperatively. Y. Passi et al, M. Das et al, A. Islam et al and M.Sinha et al had similar observations after clonidine premedication.

Just after intubation and 5 min fter intubation, the heart rate, systolic diastolic and mean arterial pressures were significantly lower in Group C compared to Group P. This is comparable to the results of the studies on effect of oral clonidine in blunting response to laryngoscopy and intubation done by Talbei et al and Raval & Mehta(18, 19).

EFFECT ON HEART RATE

The mean heart rate was significantly low in Group C at all points of time during the surgery. On insufflation, the mean heart rate was foud to be less than baseline in both groups, may be contributed to propofol anaesthesia. But, the decrease in Group C was 31.4% against a 7.27% decrease in Group P, clearly indicating the role of Clonidine premedication. Compared to baseline , significant decline in mean pulse rate was seen after 5 and 10 min of insufflation in the study by M.sinha and S.Goel(10).

Heart rate varied from 78.5 ±15.4 to 100. 9 ± 13.9(bpm) in Group P and from 63.08 ± 8.1 to 82.4 ± 13(bpm) in Group C. Y.passi et al(8) and M. Das et al(9) have obtained similar results in their placebo controlled studies and mean pulse rate was significantly low in clonidine premedicated patients at all instances noted. A. Islam et al(11) observed significant decrease in pulse rate in Clonidine group than both Atenelol and placebo. Norimasa S et al(1) also observed significantly low heart rate in patients premedicated with Clonidine than in those with Atropine Hydroxyzine at all times throughout the surgery.

EFFECT ON SYTOLIC BLOOD PRESSURE

From pre-induction to post extubation, mean systolic blood pressure was significantly lower in Group C than Group P. On induction of pneumoperitoneum, the mean systolic pressure values were found to be higher than baseline values in both groups. But, the increase was 13.95% in Group P and just 0.02% in Group C. The mean systolic blood pressure varied from 117± 20.9 to 139.6 ± 13.7(mmHg) in group P and from 102.24 ± 12.4 to 121.0 ± 15.5(mmHg) in Group C.

M. Das et al(9), Y. Passi et al(8) and Youtsi et al(14) in their studies noted a significant lowering of systolic blood pressure in patients premedicated

with Clonidine, compared to the placebo Group. Patients in the Clonidine group had significantly low systolic pressure at 5, 10 minutes after insufflations, as observed by M. Sinha and S.Goel(10). These observations correlate well with our study.

EFFECT ON DIASTOLIC BLOOD PRESSURE

Diastolic pressure also consistently remained low all through the surgery in Group C. The mean diastolic pressure varied from 79.16 ± 14.8 to 98.9± 10.8(mmHg) in Group P and from 65.72 ± 10.6 to 80.76 ± 10.1(mmHg) in Group C. On insufflation, the change in diastolic pressure from baseline was a profound decrease of up to 24.8% in Group C, while it was 19.3% higher than baseline in Group P.

A.Islam et al(11) compared Clonidine, Atenelol and Placebo for premedication in Laproscopic cholecystectomy. They observed that decline in diastolic blood pressure from baseline was more in Clonidine group and the mean diastolic blood pressure remained lower than the other groups, though not statistically significant. M .Das et al(9) , M. Sinha & S. Goel(10), Youtsi et al(14) have obtained results consistent with our observations.

EFFECT ON MEAN ARTERIAL PRESSURE

Joris et el(1) studied the hemodynamic changes during laproscopy and measured the mean arterial pressure, heart rate, cardiac output and systemic vascular resistance. 39± 8 % increase in MAP was noticed on peritoneal insufflations and they also noted a significant blunting of this response on administration of Clonidine. In our study the average mean arterial pressure varied from 95.52 ± 7.41 to 111.9 ±9.6 in Group P and from 77.8 ±10.7 to 94.9 ±14.1 in Group C. The mean arterial pressure on insufflation was 16.9% higher than baseline in Group P , while it was only 1.12% higher in Group C. This observation is supportive of the evidence that clonidine blunts the increase in MAP.

On induction of pneumoperitoneum more than 20% increase in mean arterial pressure was noted by M. Das et al(9) in placebo group, while it never crossed the baseline value in Clonidine group. A. Islam et al(11) observed a steeper decline in MAP in patients premedicated with Clonidine than in those premedicated with Atenelol or Placebo. Y. Passi et al(8) observed that mean arterial pressure was consistently lower in the clonidine group than placebo group at all points through the surgery. All these results are consistent with results of this study.

In trying to explain the hemodynamic changes during laproscopy and pneumoperitoneum, Joris et al(1) also studied the endocrine correlates of these hemodynamic changes. They found that laproscopy resulted in progressive and significant increase in plasma concentrations of cortisol, epinephrine, norepinephrine, rennin and vasopressin. Administration of 8µg/ kg clonidine as an intravenous infusion prior to surgery, significantly reduced catecholamine concentrations, but did not alter vasopressin or cortisol concentration.

Youtsi et al(14) studied the endocrine responses and concluded that Clonidine premedication prevents sympathetic hyperactivity but does not suppress hypothalamic- pitutary adrenal response to laproscopy. As we have already discussed the cardiovascular changes during laproscopy is primarily mediated by neuro humoral responses(4). The blunting of these perturbations by Clonidine consist of at least three different components(26)

A. Central activation of α -2 adrenoceptors:

    1. Reduction in peripheral sympathetic tone.

    2. Increase in vagally induced bradycardia.

B. Peripheral stimulation of presynaptic α- 2 adrenoceptors:

    3. Diminished release of norepinephrine from nerve endings.

Sung et al(12) used 150µg oral clonidine as premedicant for laproscopic cholecystectomy and concluded that it provides a stable hemodynamics. Our study results supports this conclusion.

Three patients (12%) in Group P developed hypertension. In studies by M.Das(9) et al and Y. Passi et al(8) 33%, 36% patients in placebo group required nitroglycerine for treatment of hypertension. The lower incidence in our study can be due to Propofol anaesthesia whereas Isoflourane was used for maintenance of anaesthesia in the above studies. Also MAP > 110 mmHg was treated by Y.passi, while we treated MAP > 120 mmHg.

Bradycardia was noticed in three patients(12%) in Group C and none in Group P. The incidence was 4% and 6% respectively in studies by Y. Passi et al(8) and M. Sinha & S. Goel(10) respectively. Bradycardia was transient and was easily treatable with single bolus dose of 0.6 mg of Inj. Atropine after which repeat boluses were not required.

Hypotension was noted in one patient (4%) in Group C. Y. Passi et al(8) observed a similar incidence (i.e) one out of 25 patients in clonidine group developed hypotension. None of the patients had hypotension in studies by M. Das et al and M. Sinha & S. Goel(10). The treatment required a single bolus of inj. Ephedrine 6 mg i.v and not more than that.

Other uses of clonidine in laproscopic surgeries as observed by Javaherfroosh et al(15), Talbei et al(18), Raval & Mehta(19), M Das et al(9), Y Passi et al(8), Oh SW et al(16), Youtsi et al(14), M. Sinha and S. Goel(10) are

- Sedating property
- Anaesthetic and analgesic sparing effect
- Anxolytic effect
- Reduced incidence of nausea and vomiting
- Reduced postoperative shivering
- Reduced blood sugar levels intraoperatively
- Drying of secretions.
- Blunting of hemodynamic response to intubation
- Minimal incidence of side effects which are easily treatable

Oral Clonidine is an age-old and cheap drug. Considering all these observations along with ours, oral Clonidine Premedication is definitely a cost effective method in attenuating the untoward hemodynamic changes during Pneumoperitoneum.

SUMMARY

This prospective randomised case control study was done to evaluate the efficacy of oral clonidine premedication in blunting the hemodynmic response to laproscopy and pneumoperitoneum. 50 patients of either sex, aged 16- 65 years, belonging to ASA physical status I or II undergoing either laproscopic cholecystectomy or appendicectomy were chosen for the study. They were randomised to two groups C and P, 25 patients each, to receive either Clonidine 150 μg or placebo orally as premedicant 60-90 min prior to surgey.

The hemodynamic variables heart rate, systolic, diastolic and mean arterial pressures were compared between the groups at seven points during the surgery.

- On table- before induction.
- Just after intubation
- 5 min after intubation
- 5 min after insufflation
- 15 min after insufflation
- 30 min after insufflation
- After extubation

The incidence of adverse events in the form of bradycardia, hypotension, and hypertension was noted in both groups. The results obtained were:

1. Significantly higher values of hemodynamic variables in Group P than Group C, at all the instances.
    - Mean heart rate varied from 78.5 ±15.4 to 100. 9 ± 13.9 in Group P and from 63.08 ± 8.1 to 82.4 ± 13 in Group C.($P < 0.05$)
    - The mean systolic blood pressure varied from 117± 20.9 to 139.6 ± 13.7 in group P and from 102.24 ± 12.4 to 121.0 ± 15.5 in Group C.($P < 0.05$)
    - The mean diastolic pressure varied from 79.16 ± 14.8 to 98.9± in Group C.($P < 0.05$)
    - The average mean arterial pressure varied from 95.52 ± 7.41 to 111.9 ± 10.6 in Group P and from 77.8 ± 10.7 to 94.9 ± 14.1 in Group C. ($P < 0.05$)
2. Hypertension was not seen in Group C, while 3 patients in Group P developed hypertension. However 3 patients in Group C developed bradycardia and one had intraoperative hypotension, both of which were easily treatable with drugs.

CONCLUSION

Premedication with oral clonidine 150µg , 60-90 min prior to laproscopic surgeries in adults can effectively blunt the hemodynamic response to pneumoperitoneum . Routine use can be recommended because of this advantage and minimal, easily treatable side effect profile. Further studies are needed to evaluate the usefulness of this drug as premedication for laproscopic surgeries in patients with *limited cardiac reserve.*

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PROFORMA

- Consent obtained? :
- Name of the patient:
- Age:
- Sex:
- Weight:
- Proposed Surgery:
- ASA Physical status:
- Comorbid illness:
- Time of giving clonidine / placebo:
- Time of Induction:
- Duration of surgery:

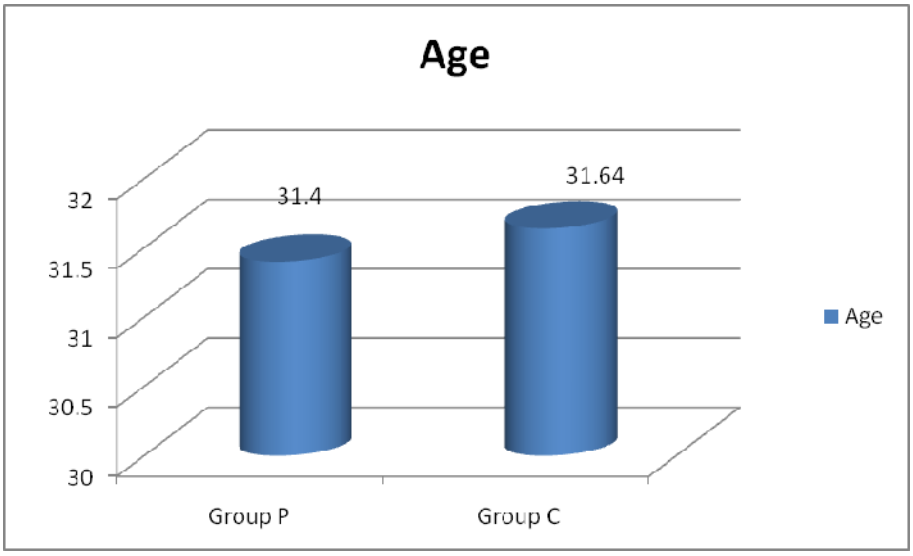
S.no	Parameters	HR	Systolic BP	Diastolic BP	MAP
1	**Before clonidine administration**				
2	**On table- baseline**				
3	**Just after intubation**				
4	**At 5 minutes after intubation**				
5	**At 5 minutes after insufflation**				
6	**At 15 minutes after insufflation**				
7	**At 30 minutes after insufflation**				
8	**After extubation**				

- Any adverse events / treatment : (Bradycardia / Hypotension / Hypoxemia)

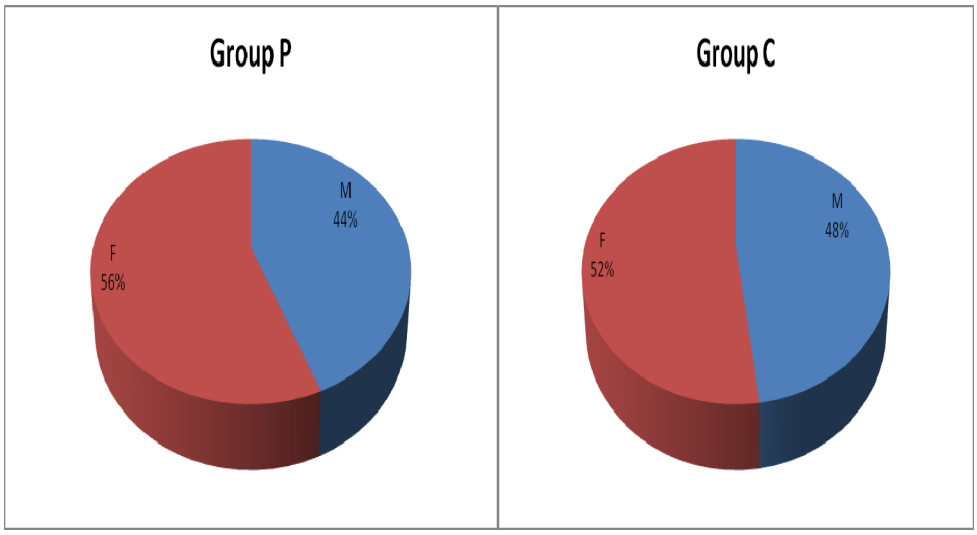
MASTER CHART

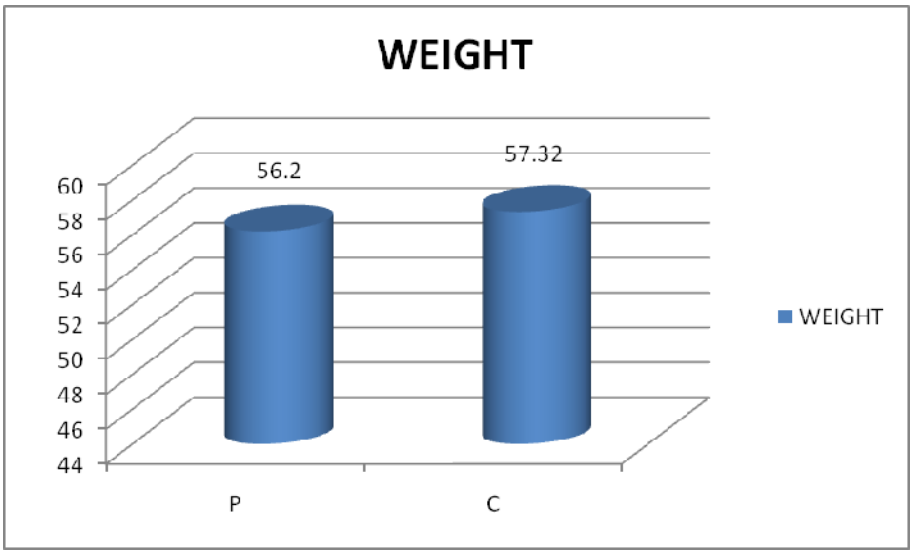
S.NO	Group	Age	Sex	Weight	Surgery	ASA-PS	Duration	HR-BSD	HR-ASD	HR-JA I	HR-5min I	HR-5min PP	HR-15min PP	HR-30min PP	HR-AE	SBP-BSD	SBP-ASD	SBP-JAI	SBP-5min I	SBP-5min PP	SBP-15min PP	SBP-30min PP	SBP- AE
1	P	55	M	67	Chole	1	78	100	102	112	108	118	101	102	102	130	130	172	170	148	144	147	138
2	P	19	F	50	App	1	46	80	88	112	84	99	96	96	109	120	122	153	99	147	144	141	136
3	P	28	M	56	APP	1	50	84	100	94	76	58	64	64	92	123	135	143	116	138	141	126	144
4	P	48	F	50	App	1	45	84	96	101	74	60	60	77	104	130	136	134	123	139	139	145	145
5	P	34	M	58	App	1	60	90	92	113	65	61	56	55	76	110	127	170	109	138	123	100	140
6	P	34	M	62	App	1	49	64	60	119	91	91	92	74	88	124	133	161	157	157	153	135	136
7	P	16	F	42	App	1	47	90	95	103	95	79	85	85	94	110	123	105	92	122	118	109	126
8	P	30	F	75	Chole	1	90	94	107	100	90	93	96	96	94	140	153	152	106	148	138	146	148
9	P	41	M	60	Chole	1	106	84	86	91	75	78	64	70	82	134	146	172	134	156	151	152	144
10	P	23	M	54	App	1	52	58	61	74	59	57	54	52	64	110	127	138	107	143	147	152	157
11	P	27	M	49	App	1	55	88	85	110	103	80	74	76	90	124	130	136	110	141	148	150	139
12	P	60	M	64	Chole	1	98	72	70	86	103	95	104	99	92	108	121	148	103	126	141	146	137
13	P	26	M	55	App	1	55	74	71	95	87	80	90	79	88	110	128	135	154	152	155	157	156
14	P	37	F	52	Chole	1	72	108	116	123	114	69	83	81	123	120	133	173	140	133	146	136	148
15	P	28	F	48	App	1	70	112	110	114	76	79	72	79	121	110	110	140	108	131	134	121	160
16	P	42	F	52	App	1	64	70	76	84	62	82	87	88	115	100	106	115	95	124	136	141	134
17	P	30	F	50	App	1	53	80	84	110	86	59	69	59	109	120	125	130	125	133	134	133	150
18	P	20	F	58	App	1	52	82	97	99	71	86	95	80	103	126	137	122	99	149	144	131	125
19	P	18	F	54	App	1	49	85	89	110	98	87	87	96	94	116	122	116	100	114	121	135	142
20	P	20	M	62	App	1	54	72	75	93	75	62	60	70	93	128	130	120	116	131	130	135	150
21	P	24	F	65	Chole	1	110	108	110	126	99	92	114	106	114	140	145	157	134	149	155	154	160
22	P	18	F	50	App	1	48	80	94	95	75	87	76	79	112	110	119	119	99	126	124	124	129
23	P	26	F	50	App	1	60	60	60	77	68	68	65	50	77	110	116	146	108	140	133	122	126
24	P	51	M	62	Chole	1	82	74	72	95	72	76	75	72	64	110	128	158	131	158	154	137	101
25	P	30	F	60	App	1	38	70	75	86	73	80	75	77	97	120	124	126	100	136	136	134	119
1	C	19	F	48	App	1	80	65	58	67	58	64	55	60	79	110	115	96	106	122	124	126	124
2	C	55	F	55	Chole	1	99	74	68	68	52	61	63	61	76	120	118	138	124	153	148	152	132
3	C	32	F	64	App	1	45	60	50	55	38	56	52	56	57	120	125	115	108	108	119	124	124
4	C	25	M	60	App	1	64	90	75	81	71	62	65	65	75	130	118	115	110	113	112	114	113
5	C	36	F	62	Chole	1	95	78	70	76	69	60	61	57	90	120	110	109	103	93	92	92	132
6	C	21	M	58	App	1	57	80	67	74	61	64	70	66	89	120	93	106	96	120	119	118	130
7	C	30	F	55	App	1	54	108	86	77	77	79	72	74	86	100	96	88	83	96	101	105	101
8	C	39	M	54	Chole	1	79	76	71	83	74	63	60	60	81	110	102	103	102	124	123	117	124
9	C	48	F	65	Chole	1	106	80	76	81	73	66	69	60	84	130	140	134	106	134	149	147	131
10	C	33	F	60	App	1	48	88	74	85	67	59	69	66	74	130	122	114	109	118	140	135	123
11	C	26	M	54	App	1	46	76	74	77	52	60	56	57	43	120	119	125	108	134	136	137	107
12	C	28	F	70	Chole	1	84	90	100	76	76	71	78	81	71	130	130	148	113	152	149	144	124
13	C	18	M	45	App	1	54	74	65	74	52	51	65	61	71	100	99	89	85	110	101	107	110
14	C	23	M	52	App	1	59	60	49	58	42	51	50	54	47	110	107	90	90	90	109	114	116
15	C	33	F	49	App	1	47	78	55	74	67	54	54	55	75	110	99	138	84	116	108	108	115
16	C	23	F	55	App	1	54	106	91	94	64	68	68	67	78	130	118	125	115	137	126	117	117
17	C	33	M	65	App	1	65	86	93	88	81	66	68	66	83	120	117	115	93	124	116	120	116
18	C	42	M	59	App	1	72	86	79	74	54	51	51	61	56	140	111	143	117	116	116	112	102
19	C	24	M	64	App	1	66	104	59	90	71	75	67	76	84	114	116	124	117	126	121	134	127
20	C	23	M	60	App	1	39	74	67	71	60	69	66	69	77	118	93	93	76	108	107	103	120
21	C	37	F	62	Chole	1	94	80	67	61	50	50	53	50	54	130	134	121	93	148	141	125	150
22	C	18	M	45	App	1	49	86	87	88	77	64	65	68	82	120	110	112	101	119	106	102	117
23	C	25	F	45	App	1	58	90	75	90	75	71	68	71	90	120	103	114	115	123	115	128	118
24	C	35	F	65	Chole	1	120	70	62	72	69	77	77	74	85	110	102	92	95	152	143	138	111
25	C	65	M	62	App	1	44	100	108	83	69	65	61	60	70	134	150	139	107	110	107	107	140

S.NO	Group	DBP-BSD	DBP-ASD	DBP-JAI	DBP-5min I	DBP-5min PP	DBP-15 minPP	DBP-30min PP	DBP-AE	MAP-BSD	MAP-ASD	MAP-JAI	MAP-5min I	MAP-5min PP	MAP-15min PP	MAP-30min PP	MAP- AE	Adv Events
1	P	90	88	111	110	95	94	96	86	103	103	131	130	113	111	115	103	Ntg-5µ/Kg/min
2	P	80	76	90	68	110	107	104	95	93	91	111	78	122	120	116	108	nil
3	P	90	90	95	76	104	102	86	95	101	105	111	89	115	115	99	112	nil
4	P	90	87	95	81	95	96	106	105	97	103	108	95	110	110	119	118	nil
5	P	80	92	120	74	92	93	72	90	90	104	137	86	107	103	81	107	nil
6	P	86	90	109	104	114	111	94	92	99	104	126	122	128	125	108	107	Ntg-5µ/Kg/min
7	P	76	82	72	65	95	90	81	91	89	95	83	74	104	99	90	103	nil
8	P	90	100	102	76	101	96	99	99	107	119	119	86	117	110	115	115	nil
9	P	86	90	108	86	113	104	103	90	102	108	129	102	127	119	119	108	nil
10	P	70	77	82	71	80	81	79	104	83	90	100	83	101	103	103	123	nil
11	P	70	80	88	74	102	107	107	94	85	96	103	86	115	120	120	110	nil
12	P	76	74	108	73	92	102	101	88	87	90	121	83	103	115	116	104	nil
13	P	80	75	80	85	92	87	92	92	90	95	98	108	112	110	114	113	nil
14	P	70	104	145	118	106	113	110	99	87	104	145	118	106	113	110	115	nil
15	P	80	76	112	75	92	96	86	100	90	87	122	86	105	109	98	117	nil
16	P	68	75	73	63	94	94	96	89	82	85	87	74	104	108	111	104	nil
17	P	80	84	105	87	100	100	96	98	93	98	113	100	111	111	108	115	nil
18	P	80	86	81	64	104	95	93	82	95	103	95	76	119	111	106	96	nil
19	P	84	85	74	68	81	84	91	104	95	97	88	82	92	96	106	117	nil
20	P	70	75	67	67	95	92	91	90	89	93	85	83	107	104	106	110	nil
21	P	90	90	107	95	99	96	99	110	107	108	124	108	116	116	117	127	nil
22	P	70	79	79	66	89	84	85	88	83	92	92	77	101	97	96	102	nil
23	P	70	73	107	71	112	90	88	81	83	87	120	83	121	104	99	96	nil
24	P	80	85	115	92	119	110	103	74	90	99	129	105	133	125	114	83	Ntg-5µ/Kg/min
25	P	80	88	90	70	96	96	95	82	93	100	102	80	109	109	108	94	nil
1	C	60	58	54	76	74	79	83	86	77	80	68	86	90	94	97	99	nil
2	C	78	67	90	70	91	89	90	91	92	84	106	88	112	109	111	104	nil
3	C	70	65	60	58	73	67	71	74	87	85	78	75	85	84	88	91	A-0.6mg (once)
4	C	90	77	77	72	75	75	72	82	103	91	90	85	87	87	84	92	nil
5	C	74	71	69	68	58	62	64	82	89	84	82	80	70	72	73	99	nil
6	C	80	59	61	51	66	73	67	78	93	70	76	66	84	88	84	95	nil
7	C	70	64	48	54	72	73	77	67	80	75	61	63	80	82	86	78	nil
8	C	70	65	71	71	85	94	84	80	83	77	81	81	105	104	95	95	nil
9	C	80	90	101	80	97	104	104	93	96	106	112	89	109	117	118	106	nil
10	C	70	72	67	66	87	87	89	77	93	98	88	80	97	104	104	92	nil
11	C	84	84	85	69	100	87	98	67	96	96	98	82	111	103	111	80	A-0.6mg(once)
12	C	80	80	84	63	90	92	88	82	96	96	104	80	110	111	101	95	nil
13	C	70	60	56	48	66	66	74	90	80	73	67	60	81	78	85	98	nil
14	C	70	63	48	55	54	75	76	72	83	78	62	66	68	86	88	86	A-0.6mg(once)
15	C	80	71	94	53	87	77	77	78	93	80	109	63	97	87	87	90	nil
16	C	90	85	89	74	12	91	81	80	103	96	99	87	114	103	93	93	nil
17	C	75	73	73	64	80	81	84	83	90	88	87	74	94	93	92	94	nil
18	C	90	77	93	83	76	76	76	62	107	88	110	94	89	89	85	75	nil
19	C	82	67	85	79	81	78	84	77	93	83	98	92	96	92	101	94	nil
20	C	70	63	64	46	78	75	69	75	86	73	74	56	85	86	80	90	E-6mg(once)
21	C	90	86	67	60	94	82	85	90	103	102	88	71	115	110	96	110	nil
22	C	80	73	75	64	85	72	72	78	93	85	87	76	96	83	82	91	nil
23	C	80	64	81	81	83	79	85	74	93	77	92	92	96	91	99	85	nil
24	C	80	72	62	65	103	101	97	82	93	85	72	75	119	115	111	92	nil
25	C	90	90	86	73	70	68	72	86	105	110	104	84	83	81	84	104	nil

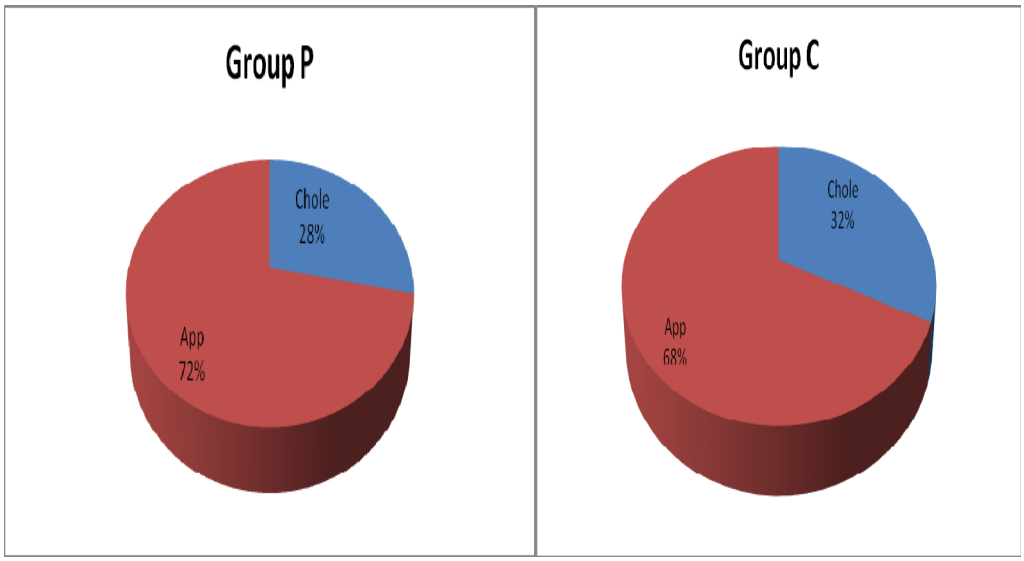


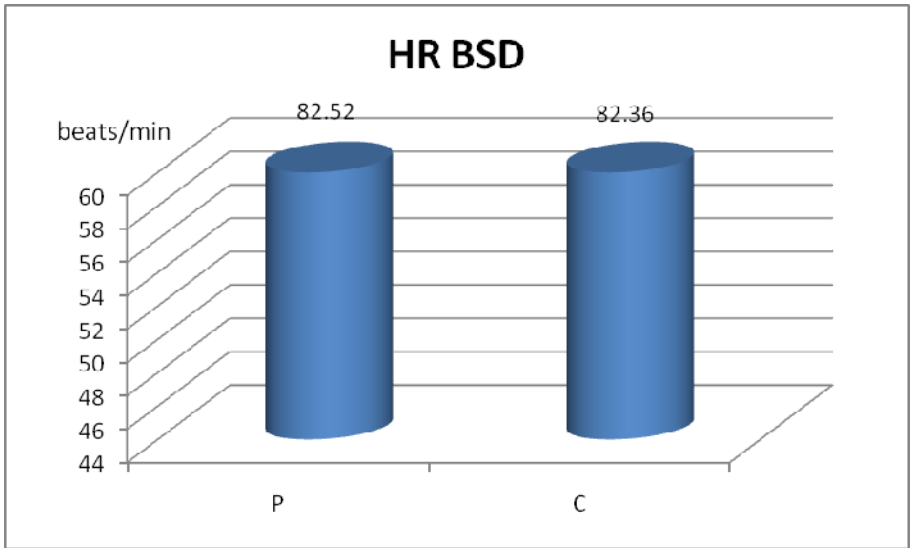
Sex distribution

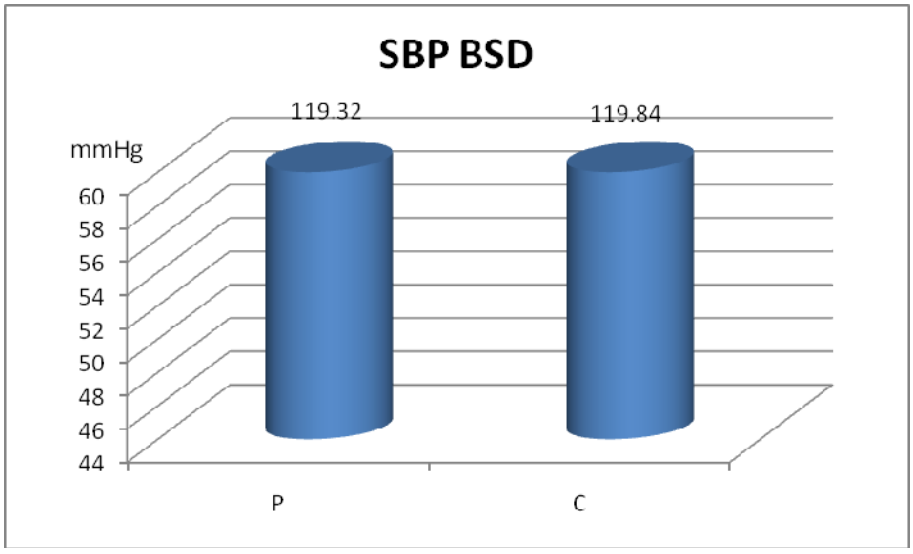




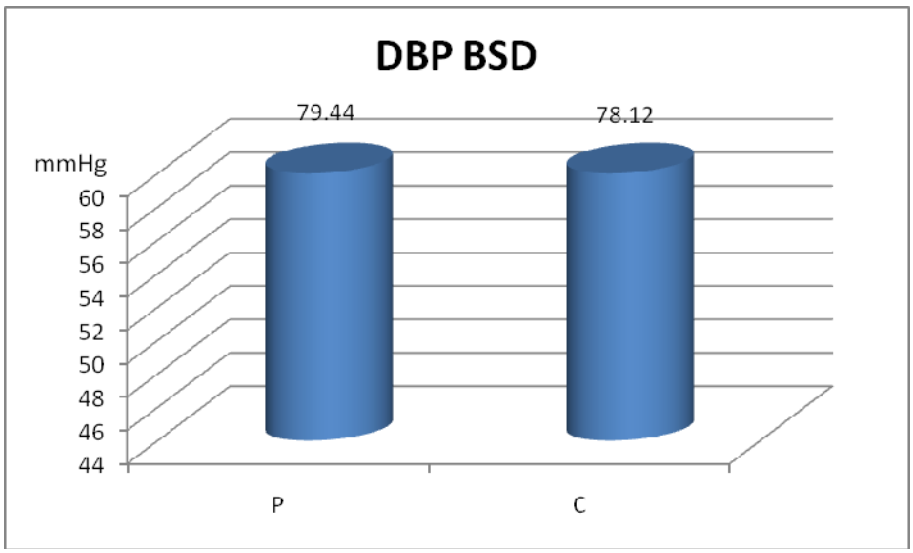
Surgical procedure

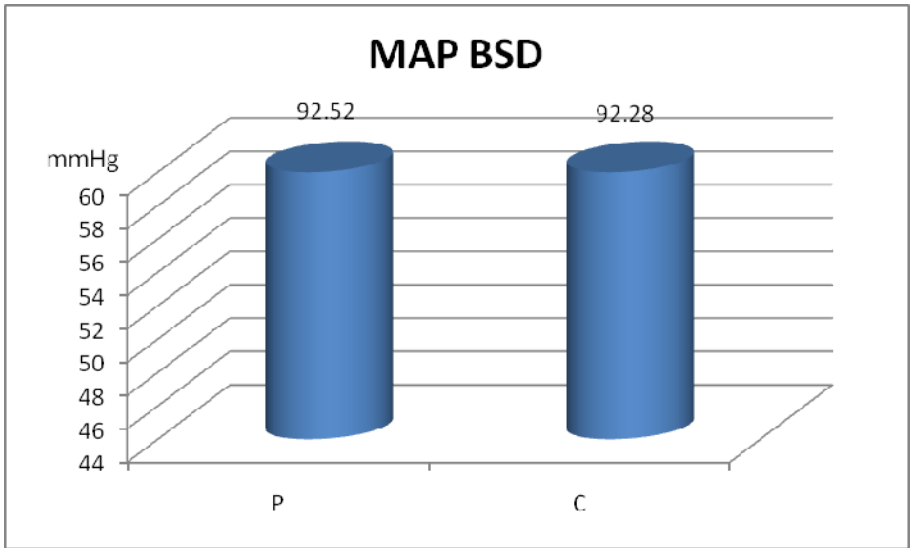




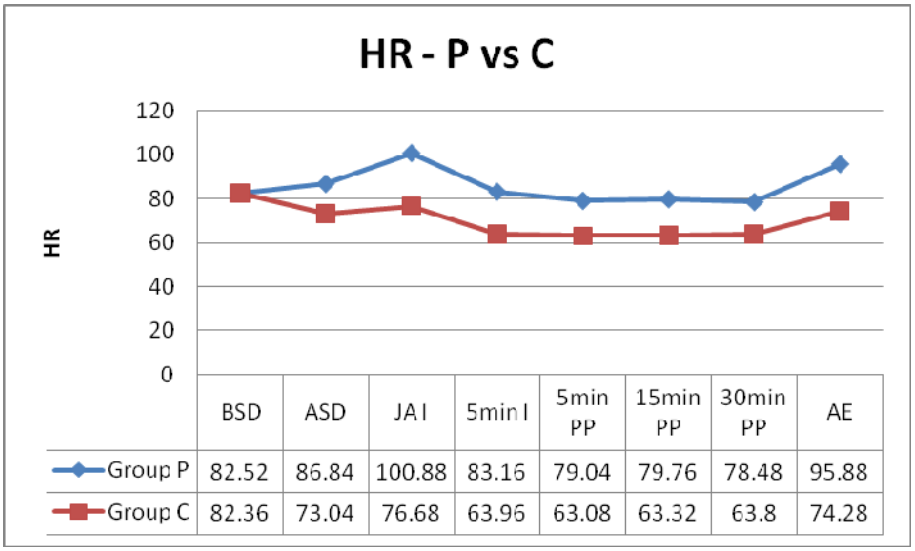


BSD – Before Study Drug

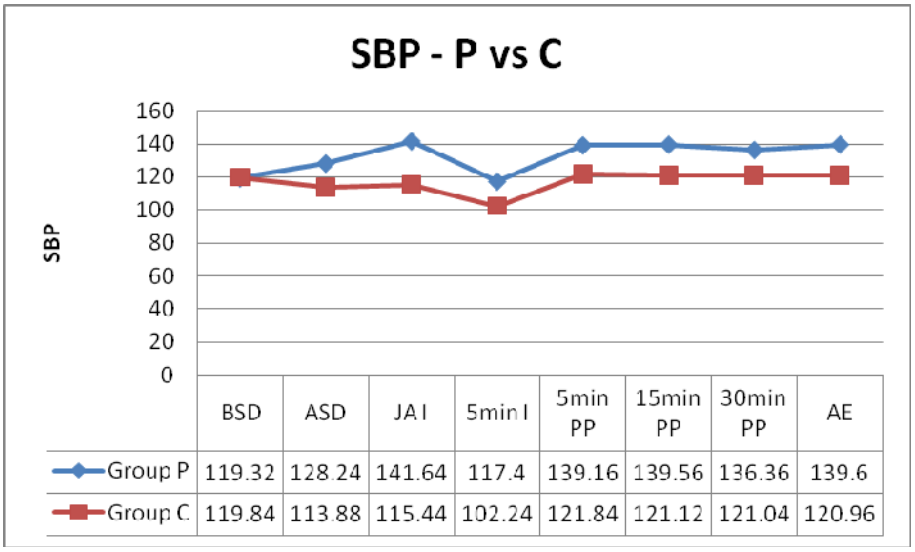




BSD – Before Study Drug



BSD –Before Study Drug
ASD – After Study Drug
JAI – Just After Intubation
5 Min I – 5 Minutes After Intubation
5 Min PP – 5 Minutes After PneumoPerotonium
15 Min PP – 15 Minutes After PneumoPerotonium
30 Min PP – 30 Minutes After PneumoPerotonium
AE – After Extubation



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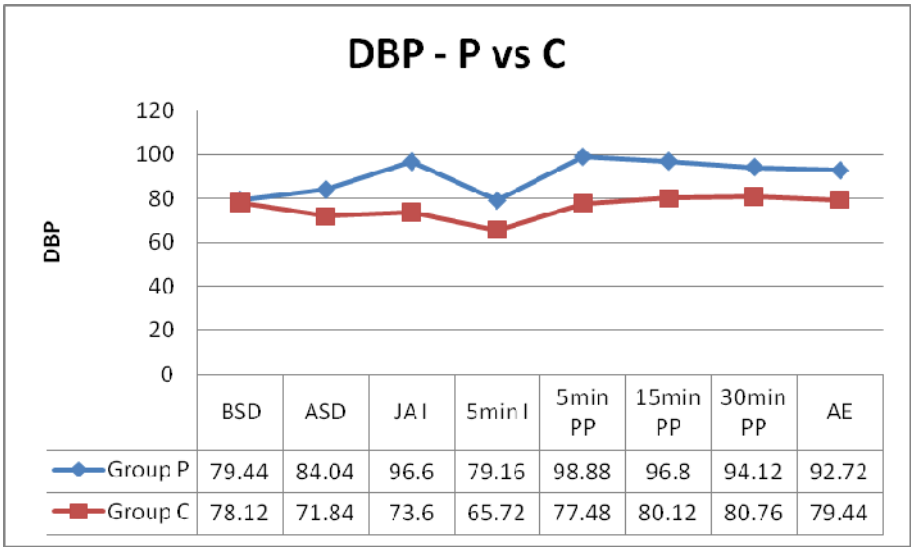

	BSD	ASD	JAI	5min I	5min PP	15min PP	30min PP	AE
Group P	79.44	84.04	96.6	79.16	98.88	96.8	94.12	92.72
Group C	78.12	71.84	73.6	65.72	77.48	80.12	80.76	79.44

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5 Min I – 5 Minutes After Intubation
5 Min PP – 5 Minutes After PneumoPerotonium
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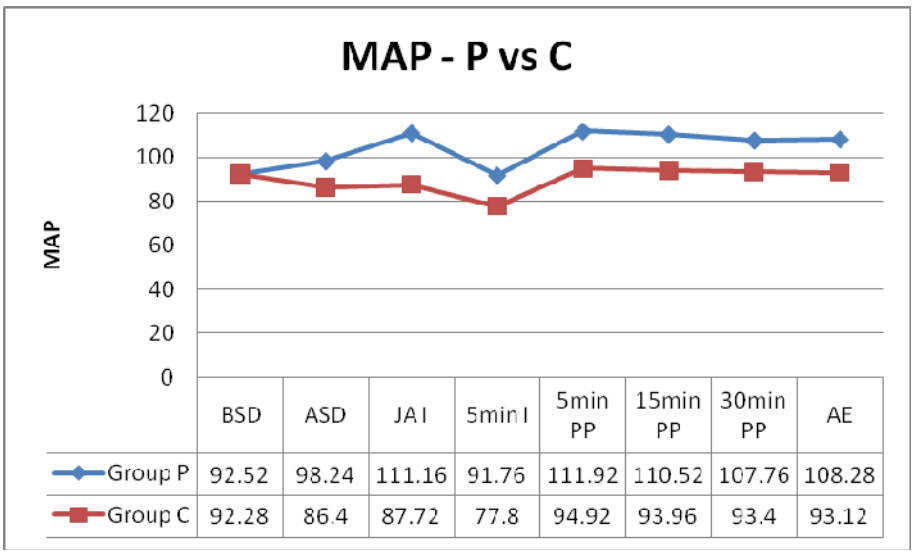
30 Min PP – 30 Minutes After PneumoPerotonium
AE – After Extubation



BSD –Before Study Drug
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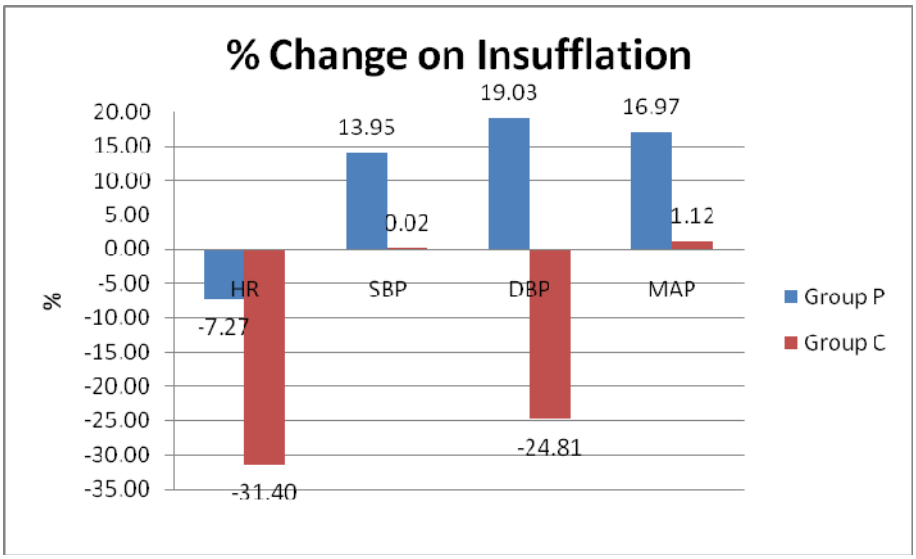
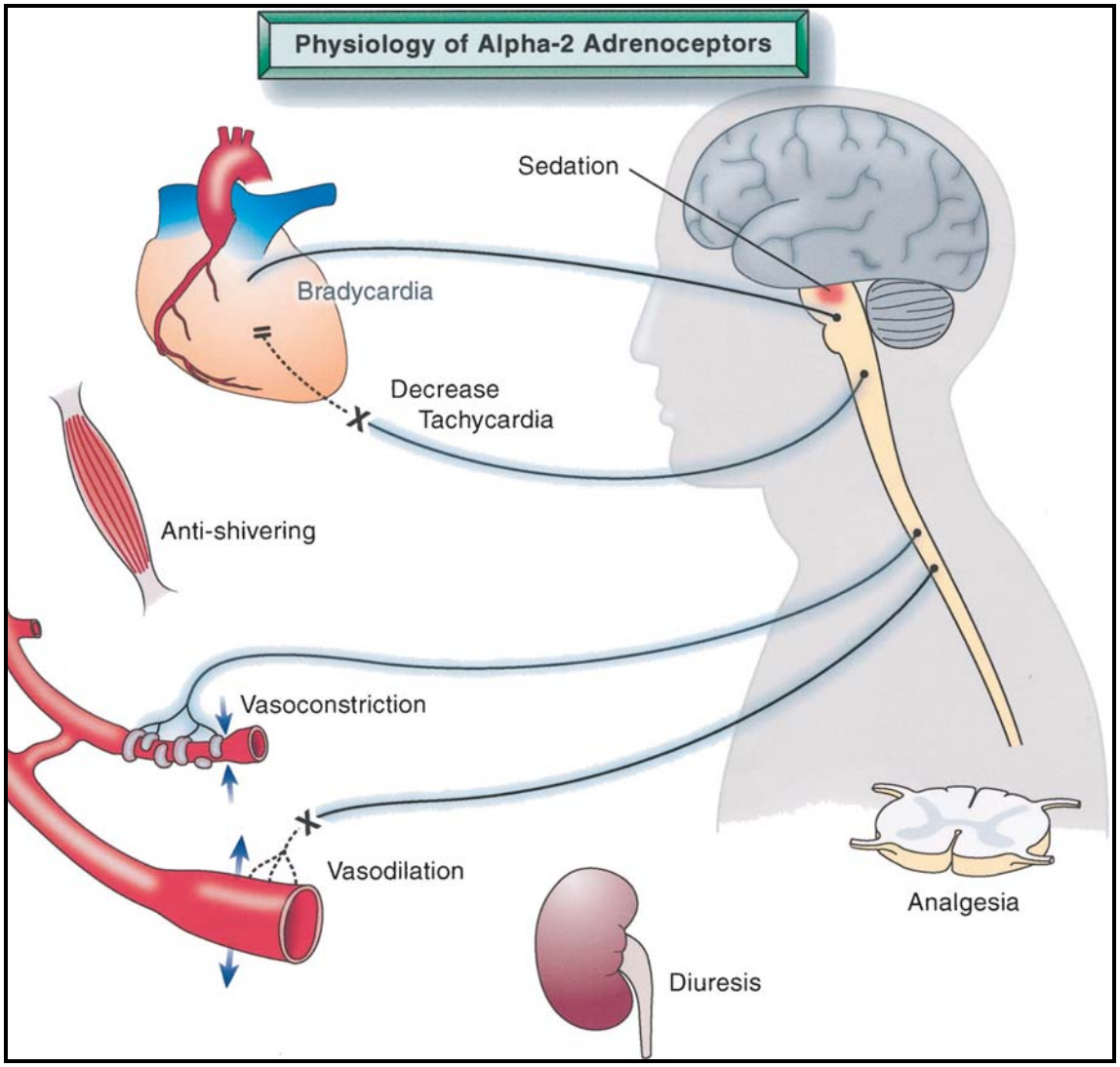

% Change on Insufflation
20.00
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
-30.00
-35.00
%
HR
SBP
DBP
MAP
-7.27
-31.40
13.95
0.02
19.03
-24.81
16.97
1.12
Group P
Group C


Physiology of Alpha-2 Adrenoceptors
Sedation
Bradycardia
Decrease
Tachycardia
Anti-shivering
Vasoconstriction
Vasodilation
Analgesia
Diuresis